

REMARKS

The present invention relates to novel cancer vaccines. More particularly, the invention relates to vaccines that include hapten-modified tumor cells for treating melanoma, and using the vaccines in a melanoma cancer patient thereby providing a therapeutic benefit.

Claims 1, 2, and 21-33 are currently pending. Claims 1 and 26 are currently amended, and claims 3-20 were canceled in a previous amendment. Claims 32 and 33 have been added and support for these claims can be found in column 4, lines 4 and 5, of original U.S. Patent No. 5,290,551. No new matter is added by way of these amendments.

Rejections

(1) The Examiner stated in the Office Action that the Oath/Declaration under 37 C.F.R. §1.175 is defective.

(2) Claim 1 stands objected to by the Examiner for a spelling error.

(3) Claims 26-31 stand rejected by the Examiner under 35 U.S.C. §103 as being unpatentable over Berd, et al. (Proc. Amer. Assoc. Cancer Res., March 1989; 30:382 Abstract #1515; "Berd 1989") in view of Berd (Cancer Investigation, 1988; 6(3):337-349; "Berd 1988").

(4) Claims 26-31 stand rejected by the Examiner as being unpatentable over Berd et al. (Proc. Amer. Assoc. Cancer Res. March 1990; 31:279, Abstract #1654; "Berd 1990") in view of Berd 1988.

(5) Claims 26-31 stand rejected by the Examiner as being unpatentable over Murphy et al. (Lab. Invest., 1990, 62(1):70A, Abstract #412; "Murphy") in view of Berd 1988.

(6) Claims 2 and 21-25 stand rejected by the Examiner as being unpatentable over Berd 1989 in view of Berd 1988 and Fujiwara (J. Immunol. 1980, 124:863-869; "Fujiwara").

(7) Claims 2 and 21-25 stand rejected by the Examiner as being unpatentable over Berd 1990 in view of Berd 1988 and Fujiwara.

(8) Claims 2 and 21-25 stand rejected by the Examiner as being unpatentable over Murphy in view of Berd 1988.

(9) Claim 1 stands rejected as being unpatentable over Berd 1989 in view of Fujiwara.

(10) Claim 1 stands rejected as being unpatentable over Berd 1990 in view of Fujiwara.

(11) Claim 1 stands rejected as being unpatentable over Murphy in view of Fujiwara.

(12) Claim 1 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 47, 65-67, 69-72, and 74-77 of co-pending U.S. Application No. 08/203,004.

(13) Claim 2 and 21-31 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 47, 65-72, and 74-77 of co-pending U.S. Application No. 08/203,004 in view of Berd 1988.

Responses

In response to rejection (1), the Applicant submits herewith a new Declaration which corrects the defects cited by the Examiner in the previous Declaration. The Applicant respectfully requests that this rejection be withdrawn. In the event that the present Declaration is not sufficient, the Applicant requests that the Examiner inform the undersigned attorney as soon as possible.

In response to rejection (2), the Applicant amends claim 1 to correct the typographical error. While the Examiner did not raise this in the rejection, the Applicant also amended claim 26 to correct the same typographical error. The Applicant respectfully requests that this objection be withdrawn.

In response to rejections (3) through (11), the Applicant presents the following arguments to the Examiner.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in any of the §103 rejections asserted by the Examiner. The MPEP states, in relevant part:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

At least one of these criteria has not been met in each of rejections (3) to (11).

With regard to rejections (3) to (5), the Examiner states that the combination of Berd 1989, Berd 1990, or Murphy with Berd 1988 renders claims 26-31 obvious because each of Berd

1989, Berd 1990, and Murphy teaches a method of treating melanoma patients with cyclophosphamide (CY) followed by autologous vaccine to induce delayed-type hypersensitivity (DTH) to melanoma cells. The Examiner further states that the method taught in these references includes administering low dose CY, and injecting patients with a vaccine of $10\text{-}25 \times 10^6$ autologous, irradiated melanoma cells mixed with BCG. The Examiner recognizes that Berd 1990 does not teach mixing the vaccine with BCG, but argues that doing this would have been obvious to one of skill in the art in order to enhance the effect of the vaccine. The Examiner states that Berd 1988 teaches administration of the vaccine in three sites on the upper arm or leg, and that it would have been obvious for a skilled person to use the method taught in Berd 1989, Berd 1990, or Murphy in conjunction with the three-site administration on the upper arm or leg. Finally, the Examiner states that the recitation that the vaccine should induce a DTH response against unmodified melanoma cells is considered to be an inherent property of the vaccine.

The Applicant respectfully traverses the Examiner's rejections. The Examiner has not met the burden of proving a *prima facie* case of obviousness because there is no motivation or suggestion to combine these references nor is there any reasonable expectation of success if the references are combined. In addition, it is asserted that the Examiner has used impermissible hindsight to combine the teachings of the cited references.

"Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). "Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). In the present Office Action, the Examiner has not demonstrated how a skilled artisan would select the elements of Berd 1989, Berd 1990 or Murphy and Berd 1988 and combine them in the manner claimed.

Berd 1989, Berd 1990 and Murphy teach use of haptanized tumor cells in a vaccine for treatment of melanoma. Berd 1988 teaches the use of non-haptanized tumor cells in a vaccine for treatment of melanoma. There is nothing in any of Berd 1989, Berd 1990 or Murphy that would motivate or suggest to one of skill in the art to combine the teachings of each of these references with Berd 1988. More specifically, there is nothing in any of these references that

would teach or suggest to a skilled person that use of haptenized cells would work in combination with the method disclosed in Berd 1988 as an effective treatment for melanoma. For these reasons, the Applicant respectfully requests that rejections (3) to (5) be withdrawn by the Examiner.

Regarding rejections (6) and (7), the Examiner states that claims 2 and 21-25 stand rejected in view of the combination of Berd 1988 and Berd 1989, or Berd 1988 and Berd 1990 with Fujiwara. The Examiner states that Fujiwara teaches conjugation of TNP to tumor cells and the use of TNP-conjugated tumor cells in treatment of tumors. The Examiner further argues that one of skill in the art would have expected that TNP-conjugated melanoma cells could be substituted for DNP-conjugated melanoma cells in order to treat melanoma.

In response to rejections (6) and (7), the Applicant respectfully asserts that the Examiner has not met the burden of proving a *prima facie* case of obviousness because there is no motivation or suggestion to combine the stated references and because there is no expectation of success in treatment of melanoma with a TNP-modified vaccine. Berd 1988, Berd 1989, and Berd 1990 relate only to DNP-modified human melanoma cells, while Fujiwara relates only to TNP-modified mouse LSTRA (leukemia) or plasmacytoma tumor cells. The tumor cells are different, and the hosts from which the cells are derived and into which the vaccines are injected are of a different species.

There is no teaching or suggestion in any of Berd 1988, Berd 1989, or Berd 1990 that any other hapten is useful for modifying melanoma cells to treat melanoma. In addition, none of the references provides any expectation of success to make or use a TNP-modified human melanoma tumor cell vaccine to treat melanoma. Likewise, there is nothing in Fujiwara that teaches or suggests haptenizing melanoma cells to treat melanoma. Further, in order to elicit a strong response, the treatment method in Fujiwara requires pre-treatment of a mouse with TNP-modified proteins to prime the mouse to generate hapten-reactive amplifier cells, followed by immunizing the mice with hapten-coupled tumor cells (p. 867, second column, first paragraph). None of Berd 1988, Berd 1989, or Berd 1990 teach priming a human patient to produce hapten-reactive amplifier cells. It is asserted that the Examiner has used impermissible hindsight to combine these references to arrive at the present invention. The Applicant contends that the Examiner has not demonstrated how a skilled artisan would select the elements of Berd 1989,

Berd 1990 or Murphy and Berd 1988 and combine them in the manner claimed. For these reasons, the Applicant respectfully requests that the Examiner withdraw rejections (6) and (7).

Regarding rejection (8), the Examiner rejected claims 2 and 21-25 as being unpatentable over Murphy in view of Berd 1988. In response to this rejection, the Applicant argues that the Examiner has not demonstrated that all of the claim limitations are disclosed by the combination of references. Neither of Murphy or Berd 1988 teach or suggest use of any hapten other than DNP to modify the tumor cells. Claims 2 and 21-25 are directed to TNP or AED-modified tumor cells. Therefore, the Examiner has not established a *prima facie* case for obviousness. The Applicant requests that this rejection be withdrawn by the Examiner.

Claim 1 stands rejected by the Examiner in rejections (9) to (11) for being unpatentable over the combination either Berd 1989, Berd 1990, or Murphy with Fujiwara. In response to rejections (9) to (11), the Applicant asserts that the Examiner has not met the burden of proving a *prima facie* case of obviousness because there is no motivation or suggestion to combine these references and because there is no expectation of success, even if the references are combined. There is nothing in Berd 1989, Berd 1990, or Murphy that would incline one of skill in the art to modify these references or combine them with Fujiwara. Berd 1989, Berd 1990, and Murphy relate only to DNP-modified human melanoma cells, while Fujiwara relates only to TNP-modified mouse LSTRA (leukemia) or plasmacytoma tumor cells. The Applicant further argues that there is nothing in Fujiwara that teaches or suggests haptenizing melanoma cells to treat melanoma. Likewise, there is no teaching or suggestion in any of Berd 1989, Berd 1990, or Murphy that any other hapten is useful for modifying melanoma cells to treat melanoma. In addition, none of the references provide any expectation of success to make or use a TNP-modified human melanoma tumor cell vaccine to treat melanoma. For these reasons, the Applicant respectfully requests that the Examiner withdraw rejections (9) to (11).

With regard to rejections (12) and (13), where the Examiner provisionally rejected certain claims of the pending application in view of certain claims in U.S. Application No. 08/203,004, the Applicant hereby agrees to file a terminal disclaimer to any patent that issues from U.S. Application No. 08/203,004 if the claims of the issued patent still raise a double-patenting issue for the Examiner.

Summary

Applicant respectfully submits that each rejection of the Examiner to the claims of the present application has been either overcome or is now inapplicable, and that each of claims 1, 2, and 21-33 is in condition for allowance. Reconsideration and allowance of each of these claims are respectfully requested at the earliest possible date.

Respectfully submitted,
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Enclosures (Reissue Declaration and Petition for three-month extension of time and associated fee)